Association of Intracranial Hypertension With Calvarial and Skull Base Thinning

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ABSTRACT

Objective: Determine if patients with increased opening pressure (OP) on lumbar puncture (LP) have thinner calvaria and skull bases.

Study Design: Retrospective Cohort Study

Setting: Tertiary Referral Center

Patients: Patients (≥18 years of age) who had a recorded OP on LP and high-resolution CT imaging of the head. Patient age, gender, body mass index (BMI) were calculated. Intracranial hypertension (IH) was defined with an OP≥25 cm-H_2O and low intracranial pressure with an OP<15 cm-H_2O.

Intervention: Measurement of calvarial, zygoma, and skull base thickness when blinded to OP with 3D slicer and radiologic calipers.

Main Outcome Measures: Association of calvarial, skull base, and zygoma thickness with OP and age.

Results: 58 patients were included with a mean [SD] age of 53.1 [16.2] years and average [SD] BMI of 30.1 [9.1] kg/m^2. Patients with IH had thinner mean [SD] calvaria (3.01 [0.81] vs. 2.70 [0.58] mm; p=0.036) and skull bases (5.17 [1.22] vs. 4.60 [1.42] mm; p=0.043) when compared to patients without IH. The mean [SD] extracranial zygoma thickness was similar between the 2 groups (5.09 [0.76] vs. 5.00 [0.73] mm; p=0.56). General linear model regression demonstrated advancing age was associated with increasing calvarial thickness in patients without IH and calvarial thinning in patients with IH (p=0.038).

Conclusions: IH is independently associated with intracranial bone (calvaria and skull base) thinning and not extracranial (zygoma) thinning. Skull thinning occurs with IH and advancing

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age. These findings support a possible role of increased ICP in the pathophysiologic development of spontaneous cerebrospinal fluid leaks.

INTRODUCTION

Spontaneous cerebrospinal fluid (sCSF) leaks are a disease state whose rates have increased by more than 100% in the past decade, concurrent with the rise of the obesity epidemic(1). They are most common in obese, middle-aged (45-65 years) females(2,3). While the exact mechanism of sCSF leaks is not completely understood, it is known that patients with this disease have defects in the bone of the skull base as well as in the dural lining of the brain without an obvious inciting factor. The patients also have thinner calvaria compared to matched controls, although the extracranial zygoma remains unaffected(4). A probable explanation for this discrepancy in bone thickness is the presence of an intracranial process that causes thinning of the calvarium(5).

Elevated intracranial pressure (ICP) may be the culprit. Elevated ICP has been documented in about 36% of patients with sCSF leaks(6). ICP can be intermittently or persistently elevated. Some have proposed that obesity may lead to increased intraabdominal and intrapleural pressures, leading to increased cardiac filling pressures and ultimately causing cerebral venous retention and elevated ICP(7). A positive linear relationship has been shown between CSF pressure and BMI, with a 0.24 mm Hg increase in CSF pressure per unit of BMI(6). A previous study from our institution examined skull thickness in non-CSF leak patients with obstructive sleep apnea (OSA)(8), since OSA is known to cause intermittently elevated ICP during apneic episodes(9) and 83% of patients with sCSF leaks also have OSA(6,10). The study found that non-sCSF leak patients with OSA had thinner skulls than age and BMI matched controls(8). Conversely, a phenomenon called hyperostosis cranii ex vacuo has been shown to be a rare complication of patients who have been shunted for hydrocephalus(11); these chronically shunted patients have been shown to have diffuse thickening of the skull(11).

Our study examines the hypothesis that increased ICP can lead to skull thinning by evaluating the thickness of the calvarium on radiologic imaging of patients with measured ICP based on lumbar puncture (LP). This study aims to further elucidate the link between increased

ICP and skull thinning, a link which may further clarify the relationships between obesity, increased ICP, and sCSF leaks.

METHODS

Patient Selection

After institutional review board approval (IRB 1707295676), the Cerner IU Health database was searched for all patients who underwent an LP from January 2008 to December 2017. Of this initial data set, patients with a documented opening pressure (OP) and those with a previous CT Maxillofacial Area/Sinus, CT Paranasal Sinuses, or CT Internal Auditory Canal (IAC) were then selected (**Figure 1**). These scans were chosen due to their high probability of being high-resolution thin-cut CT scans, with ≤1 mm axial and coronal sections.

These patients were then chart-searched for OP of LP as well as age, BMI, race, and relevant diagnoses that had been entered into the medical record (obstructive sleep apnea [OSA], diabetes mellitus [DM]). Only white patients were included in this study due to the relatively low number of black patients available for analysis. Patients less than 18 years old were excluded as well as LP's performed in the setting of traumatic or infectious pathology. Patients with the presence of an intracranial shunt were also excluded. In this initial patient selection process, our criteria ultimately yielded 58 patients with a diagnostic LP and an acceptable high-resolution CT scan of the head.

Radiologic Analysis and Measurements

Patient CT scans were downloaded, de-identified and randomized for measurement. All measurements were performed when blinded to OP. CT scans with ≤1 mm slice thickness were used. Measurements were performed using 3D Slicer 4.6.2, an open source, NIH-funded image analysis tool. The method used was developed during a previous study from our institution which examined skull thickness in OSA patients(8). The method was precise and accurate for measuring calvarium and zygoma thickness. Zygoma thickness served as an internal control for our study, since the zygoma is extracranial and therefore not subject to intracranial forces. Patient scans were measured bilaterally, with n = number of measurements, therefore giving 2 measurements per patient.

Calvarial thickness measurements were obtained in the coronal plane. Calvarial thickness was measured from just anterior to the foramen rotundum. A threshold of 400 Hounsfield units was applied for highlighting bone, and 15 mm in height of the thinnest part of the calvarium was selected and highlighted. From here, 15 mm segments of calvarium were highlighted on each CT slice as the scan moved posteriorly (**Figure 2**). Care was taken to highlight only the thinnest portion of the calvarium, while avoiding air cells. This highlighting process continued posteriorly until the level of the superior portion of the semicircular canal was reached. 3D slicer calculated this length of bone measurement, and the volume of the bone was found using 3D slicer's volume analysis tool. Measurements were performed bilaterally, yielding a total of 116 measurements (n = 116) on 58 patients. As the volume, length and height was known at this point, the following calculation was used to determine the calvarium thickness on each side: Calvarium Thickness = Volume / [Height x Length]. These values were averaged to obtain the overall average calvarium thickness.

The zygoma was measured using the same 400 Hounsfield unit threshold. It was measured along a 5 mm posterior spanning anterior to posterior along the zygomatic process just anterior to its attachment to the temporal bone, as seen on coronal scans. This was measured as an internal imaging control as it was a consistent extracranial bone that was seen in all scans we used. After highlighting the slices needed to reach about 5 mm in length, the volume was obtained using 3D slicer's volume analysis tool. The number of slices was multiplied by the thickness of each slice and this value was about 5 mm for each measurement. Lastly, the zygoma was treated as a cylinder and the following calculation was used to determine zygoma thickness: Zygoma thickness = $2 * (\sqrt{} (\text{Volume} / (\text{length} * \pi))$.

Skull base measurements were obtained by measuring the height of the internal auditory canal (IAC) in the coronal plane. The caliper measurement tool was used to measure the bone over the IAC at the level of the labyrinthine segment of the facial nerve as it entered the

fallopian canal on coronal images (**Figure 3A & B)**. These measurements were performed bilaterally. If the IAC was not included on the scan, the scan was excluded from this analysis.

Because there were slight differences between CT Maxillofacial studies and CT Internal Auditory Canal, a correction factor was used to normalize the measurements for calvarium and zygoma thickness in CT IAC scans. This correction factor was calculated in a previous study from our institution by using scans from five patients with both types of scans within a six-month period to measure both calvarium and zygoma. The measurement values were averaged, and their difference was calculated in order to calculate a correction factor. The correction factor was calculated to be 15.5% for calvarium thickness measurements and 5.05% for zygoma thickness measurements. This was applied to all CT IAC scans that were measured.

Validation Measures

The intraclass correlation coefficient (ICC) was calculated to determine the interrater reliability of 2 independent raters. For the assessment, a total of 20 patients' CT scans were analyzed. Four measurements were obtained from each scan (right zygoma, left zygoma, right calvarium, left calvarium). The raters were blinded to each other's measurements. SPSS was used to analyze the ICC using two-way mixed model for absolute agreement. The strength of agreement were calculated for each measurement and can be interpreted as follows: <0.5 = poor reliability; 0.51 – 0.75 = moderate reliability, 0.76 – 0.9 = good reliability, 0.91-1.00 = excellent reliability(12).

Statistical Analysis

Data was aggregated utilizing Excel 2013 software (Microsoft Corp). Statistical analysis was performed to determine the existence of significant differences between the measurements and demographic patient data obtained. SPSS software (version 24, IBM Corp.) was used for all data analysis. Two-tailed independent samples T-tests, Effect Size, Pearson correlation, and General Linear Model regression analysis were applied. For regression analysis we calculated R^2 values, coefficient of determination representing how close the data are to the

fitted regression line. For all other tests, 95% confidence intervals (CIs) were used to inform statistical and clinical significance. Cohen *d* was used as a measure of effect size where indicated. Based on Cohen *d*, we consider $d = 0.2$ to be a small effect, $d = 0.5$ to be moderate effect, and $d \geq 0.8$ to be large effect. For regression analysis, p values < 0.05 were considered statistically significant.

RESULTS

We searched the medical record over a 10-year period (January 2008 to December 2017) and found 13,878 patients who had undergone a lumbar puncture. Next, we identified 598 of those patients who had also had a high-resolution head CT during that time period. After additional exclusion criteria we obtained a cohort of 58 patients (**Figure 1**). It should be noted that 10 black patients were excluded because black patients have significantly thicker calvaria and zygomas compared to whites (data in review). The majority of patients underwent LP for work up of headache, altered mental status, seizures and new neurologic deficits (**Table 1**); with patients whose cultures revealed bacterial meningitis excluded from the final cohort.

There were 21 males and 37 females with an overall mean age [SD] of 53.1 [16.2] years and mean body mass index [SD] of 30.8 [9.1] kg/m^2 (**Table 1**). Co-morbid conditions that could be identified in the medical record included type II diabetes in 16 patients and OSA in 7 patients (**Table 1**). It is unknown what the true prevalence of OSA in this cohort since we did not perform formal sleep testing on all patients. One patient included in this cohort was ultimately diagnosed with a spontaneous CSF fluid leak repair prior to the LP but after the initial CT scan.

Calvarium thickness and zygoma thickness measurements were obtained from high resolution CT scans (≤1 mm slice thickness) using 3D slicer (**Figure 2A & B**). The total number of measurements was 116 as we obtained bilateral measurements of the calvarium and zygoma for each patient. The absolute value average [SD] time between the date of the high-resolution CT and LP was 15.0 [18.0] months. The date of the LP was >3 months before the date of the CT in 23 patients, within 3 months in 20 patients and >3 months after the CT in 15 patients.

We validated the reproducibility of 3D slicer program for calvarial and zygoma measurements between 2 individuals who were blinded to the diagnosis or the other measurements. The interclass correlation coefficient (ICC) for the calvarial thickness was excellent at 0.974 (95% CI, 0.952 – 0.986) (**TABLE 2**) and the ICC for the zygoma thickness was excellent at 0.994 (95% CI, 0.988 – 0.997) (**TABLE 2**).

We first evaluated the effect of OP on zygoma and calvarium thickness. We found no correlation between the extracranial zygoma thickness and OP (Pearson = -0.055, p = 0.558). However, there was a near significant trend toward thinning of the calvarium with increasing OP (Pearson = -0.16, p = 0.081). Subgroup analysis was performed comparing those with the lowest OP (<15 cm H_2O) to those with the highest OP (≥25 cm H_2O). Patients with the highest OP had significantly thinner mean [SD] calvarial thickness compared to those with the lowest OP (3.01 [0.81] vs. 2.70 [0.58] mm; difference, -0.31 mm; 95% CI, -0.60 to -0.02; Cohen *d* = 0.44, **Figure 2D**). As an extracranial control, the mean [SD] zygoma thickness was not significantly different between the 2 groups (5.09 [0.76] vs. 5.00 [0.73] mm; difference, -0.085 mm; 95% CI, -0.39 to 0.22, **Figure 2C**).

Next, we determined if high OP was associated with skull base thinning. IAC height was subsequently measured in these groups as a representation of skull base thickness (**Figure 3A & B**). Patients in the higher OP group had a significantly thinner average skull base [SD] than those with lower OP (5.17 [1.22] vs. 4.60 [1.42] mm; difference, -0.57 mm; 95% CI -0.022 to 1.12; Cohen *d* = 0.43, **Figure 3C**).

Next, we sought to perform the analysis controlling for patient related factors including BMI, age, gender, OSA and diabetes. Seven patients had the diagnosis of OSA in the medical record. The range of OP was 14-28 cm H_2O in patients with OSA with only 2 patients having OP ≥25 cm H_2O. We used general linear model regression analysis to evaluate the effect of OP on zygoma thickness and calvarium thickness when controlling for patient related factors. Again, we found that OP has no effect on zygoma thickness (p = 0.80). No significant effect of OP alone was found on calvarium thickness (p = 0.13); however, we discovered that age impacts our statistical analysis and the calvarium thickness results. In patients with OP <15 cm H_2O, the calvarium thickness increased with advancing age (R^2 = 0.26, **Figure 4**); and, in patients with OP ≥25 cm H_2O, there was significant decrease in calvarium thickness with advancing age (p = 0.038, R^2 = 0.39, **Figure 4**).

Finally, this analysis also revealed diabetic patients had thicker calvarium while maintaining persistent skull thinning with increased OP ($p < 0.01$); but diabetes was not associated with any changes in zygoma thickness ($p = 0.14$).

DISCUSSION

In this cohort of middle-aged white patients, an opening pressure of ≥25 cm H_2O is associated with calvarium thinning and this effect is more robust with increasing patient age. Interestingly, there was a thickening of the calvarium with increased age in patients with lower ICP (<15 cm H_2O). This effect from opening pressure was not identified on extracranial zygoma. The cut off for the high ICP group (≥25 cm H_2O) was chosen based on the Dandy criteria used in the diagnosis of idiopathic IH(13,14). This trend toward thinning with increased OP was initially identified by correlation relationship, and further teased out with subgroup and linear regression analysis. A measure of effect comparing average calvarium thickness in high and low-pressure groups was represented by the Cohen *d* calculation; and this revealed a medium effect size reinforcing the significance of this finding. These subgroups were further examined with measurements of the skull base thickness (represented by IAC height), revealing a significant thinning with the higher OP group. And once more, a medium effect size was found for the impact of OP and skull base thickness.

Our method for skull and zygoma measurements is non-biased, highly accurate and reliable. The ICC correlation for both measurements is >0.97 which demonstrates excellent reliability. Previous methods of measuring the lateral skull base using calipers demonstrated an ICC measurements ranging from 0.14 to 0.85(15). The reliability decreased in patients with very thin skull bases(15). Similar to previous studies from our institution(4,8) the thickness of the squamous portion of the temporal bone is used as a surrogate for global calvarium thickness and the IAC height for skull base thickness. Given this link of calvarial thickness to skull base thickness, use of the highly accurate 3D slicer method described here is recommended for future studies.

At the initial start of this study we sought out to investigate the role of ICP in skull and skull base thinning, and ultimately how this may play a role in the formation of a sCSF leak. The intracranial processes leading to sCSF leaks have yet to be identified but elevated ICP has

been shown in patients with sCSF leaks along with associated symptoms including vertigo, tinnitus, and headaches(16,17). Like patients with IH examined in this study, it has been shown that patients with a sCSF leak have global thinning of the calvarium without thinning of the extracranial bones(4). Patients with sCSF leaks are typically obese (average BMI = 38 kg/m^2), female (72%) and middle age (45-65 years)(2). Similar to findings in another published study from our institution(8), we found that BMI alone was not associated with calvarium thinning; this is a finding consistent with previous studies that have suggested that obesity-related factors, rather than obesity itself, are potential causes of skull thinning(1,8).

Age has previously been shown to correlate with superior semicircular canal (SSC) roof height(18,19), revealing a reduction in height with increased age. Regarding age, we did not find an independent relationship between skull thickness and age but rather an interaction between age and ICP. In patients with normal ICP, the calvarium thickness increased with aging; while the calvarium thickness decreased with aging in patients with high ICP. Systemic bone metabolism conditions (e.g. osteoporosis, post-menopause estrogen deficiency) could be theorized to impact skull thickness. The current study design prohibited true measures of systemic bone mineral density in our cohort. However, if a systemic disease was a confounding factor, the extracranial zygoma should also be altered in a similar way as the calvarium. Thus, having the same average zygoma thickness between groups suggests that the calvarial thinning in our cohort is not from a systemic bone metabolism condition. Interestingly, we identified an overall thicker skull in patients across all ages with type 2 diabetes mellitus. While this effect is not fully understood at this time, insulin related growth factors may be culpable. An isolated cohort of matched diabetic and non-diabetic patients would be needed to definitively show an impact of diabetes on calvarium thickness

OSA has an association with obesity and has been shown to cause transient elevations in ICP during apneic episodes(5,20). A recent study found the prevalence of OSA among sCSF leak patients is 83%(10). OSA has now been shown to be independently associated with skull

and skull base thinning(8). This relationship is theorized to be associated with transient elevations in ICP previously shown in patients with OSA(5,20).

We now may add IH to OSA as an obesity-related factor linked with skull and skull base thinning. These findings suggest that elevated ICP may increase the risk of developing sCSF leaks. Notably, skull base erosion and thinning to a magnitude of <1 mm may be sufficient to cause CSF leaks in inherently thin portions of the skull base, such as the fragile cribriform plate or bony areas overlying the pneumatized recesses(1). Our data shows that elevated ICP and sCSF leak patients fall on a continuum of skull thinning, while their zygoma thickness measurements are not affected. These findings add to the discussion regarding the relationship of obesity, OSA, and ICP with sCSF leaks.

Limitations

A potential limitation of this study is a relatively low sample size in our final groups relative to our initial large number of patients. However, this relatively low sample size was inevitable; we aimed to control for numerous variables to investigate the independent effect of ICP on calvarium and zygoma thickness, and to do so required strict criteria for patient inclusion. The inherent variability in calvarium and zygoma thickness across all patients is a known limitation; a larger sample size would be required to strengthen this study and its findings. Another potential limitation was our decision to exclude black patients. This study solely focuses on white patients given the low number of African American patients and the potential impact of race on differences in bone thickness. Future studies investigating the skull thickness differences and prevalence of sCSF leaks in white and black populations would be valuable. It should be highlighted that the cohort of patients examined in this study had lower average BMI and a lower average age compared to those with sCSF leak. It may be speculated in an older age group of patients with elevated ICP, we could expect a more substantial thinning of the calvarium.

Another potential limitation of our study is the inclusion of multiple types of scans which could inherently have differences between them. However, we accounted for this by utilizing a correction factor to augment the CT IAC measurements, and this likely strengthened our data. By augmenting the CT IAC measurements, the predominant study ordered for sCSF leak patients, we were able to compensate for any intrinsic aspect of the scans that could yield a lower measurement in this subgroup.

It should also be considered that the ICP fluctuates regularly throughout the day. By utilizing OP on an LP as a variable to represent ICP, we depend on a single time point when the LP was performed. Monitoring the ICP continuously in the setting of the objectives of this study would be difficult to accomplish and rather invasive to perform. It is worth highlighting that it is unknown how long patients in this cohort had been affected by elevated ICP, data which is unobtainable without multiple time points and LP's performed throughout a patient's lifetime. The timing between the CT scan and the LP also varied between patients. However, 20 out of 58 patients had both the CT and LP within a 3-month time period. The other patients were relatively equally distributed with having the LP either >3 months prior or >3 months after the CT. We also exclude patients who have had any ventricular shunting procedures performed so the potential effects of CSF pressure changes are not reversed if the CT scan is performed at a later date.

Finally, we are limited by our ability to account for other potential causes of skull thinning that are yet to be discovered. We controlled for variables including age, race, BMI, and co-morbidities, but ultimately there are some variables for which we cannot account. The role that other disease pathologies such as diabetes mellitus, OSA, and osteoporosis may play has yet to be investigated. For example, a majority of these patients did not have formal polysomnograms to evaluate for OSA, which has been identified as a factor independently involved in skull thinning(8,10). Thus, we were not able to delineate the relationship between OSA and increased ICP within our study patients. Ultimately, the development of sCSF leaks is

likely a multi-factorial process and we believe that both ICP and OSA are important factors among others.

CONCLUSION

By analyzing the CT scans of patients with a formal LP, we found a significant effect of ICP on calvarium and skull base thinning. ICP likely plays a role in the pathophysiology of skull and skull base thinning and ultimately may contribute to the development of sCSF leaks. Future studies are needed to identify the mechanism of how increased ICP may lead to skull thinning and how this may increase the risk of sCSF leaks. Future studies may reveal the utility of radiologic skull measurements as predictors of elevated ICP and OSA. Future studies may also reveal other factors contributing to the development of sCSF leaks.

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FIGURE LEGENDS:

FIGURE 1 – Patient Selection Flow Chart

Patients were identified by first searching for all patients who underwent a LP in the past few years. There were 598 patients with an LP and a high-resolution CT scan of the head available for measurements. From these patients, 58 patients were ultimately selected for final analysis after several exclusion steps, as shown above. LP = lumbar puncture

FIGURE 2 – Calvarial Thinning in Patients with Intracranial Hypertension

(**A**) Measurements were taken in the coronal plane of a 15-mm (mm, height) segment of the thinnest portion of the squamous temporal bone. Segments were highlighted bilaterally, starting at the level of the foramen rotundum anteriorly and extending posteriorly to the level of the upper superior semicircular canal. Volume was calculated using 3D Slicer's volumetric analysis tool (version 4.6.2, http://www.slicer.org). (**B**) A 3-dimensional reconstruction illustrating the highlighted calvarium segment. (**C**) Comparison of zygoma thickness between patients with low OP and high OP. (**D**) Comparison of calvarial thickness between patients with low OP and high OP. OP = opening pressure; d = Cohen's d; NS = non-significant, mm = millimeter; cm = centimeter

FIGURE 3 – Skull Base Thinning in Patients with Intracranial Hypertension

(**A & B**) Representative CT images of skull base measurement from patients with low opening pressure and high OP. (**C**) Comparison of skull base height between patients with low and high OP. OP = opening pressure; d = Cohen's d; NS = non-significant; IAC = internal auditory canal; mm = millimeter; cm = centimeter

FIGURE 4 – Effect of Opening Pressure and Age on Calvarium Thickness

General linear model univariate regression analysis of the relationship between opening pressure, calvarium thickness and age. Prediction of calvarial thickness with advancing age in patients with low OP (grey circles) and high OP (black squares). OP = opening pressure; mm = millimeter; cm = centimeter; y = years